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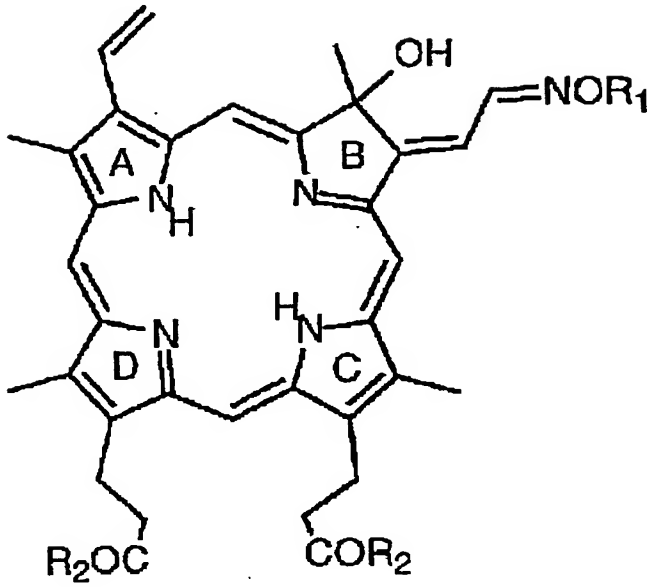
TITLE : PORPHYRIN DERIVATIVE AND USE THEREOF



ABSTRACT : PROBLEM TO BE SOLVED: To provide the above compound having accumulation property to cancer cell, reactivity to external energy and destructing action on cancer cell, free from toxicity to normal cells and useful as an agent for the treatment or the diagnosis of cancer.

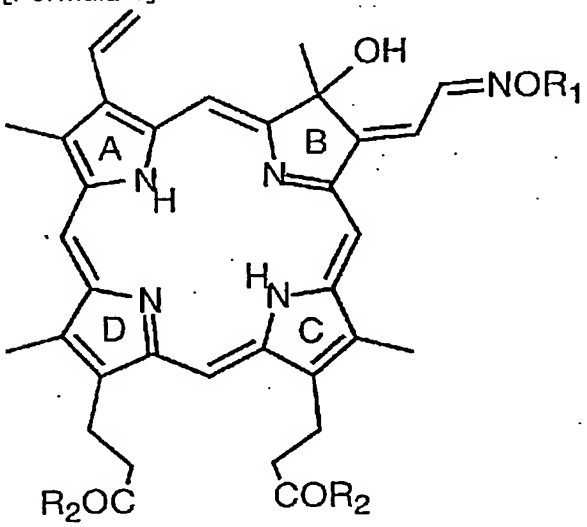
SOLUTION: This porphyrin compound is expressed by the formula [R_1 is CH_3, C_2H_5, $CH_2CH(CH_3)_2$, $CH_2C_6H_5$ or $CH_2C_6F_5$; R_2 is a residue produced by removing H from aspartic acid) (including position isomers obtained by exchanging the functional groups of the side chains on the rings A and B among four tetrapyrrole rings in the formula), e.g. 13, 17-bispropionylaspartic acid-3-ethenyl-7-hydroxy-8-methoxyiminoethylidene-2,7,12,18-tetramethyl-porphyrin. The compound of the formula can be produced, e.g. by producing a chlorin derivative having corresponding aldehyde group, bonding an aspartic acid residue to the derivative and condensing the product to a hydroxylamine derivative.

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

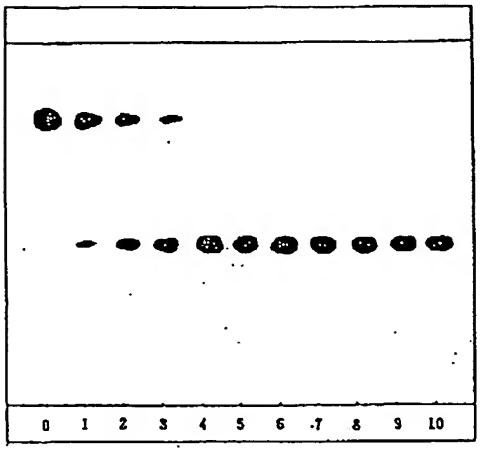
[Claim(s)]
[Claim 1] General formula (I) Porphyrin compound shown by-izing 1 (inside of a formula, residue excluding [CH3, C2H5, CH2CH (CH3)2, CH2C6H5, CH2C6F5, and R2] hydrogen from the aspartic acid in R1). (However, the functional group of the side chain of B ring also contains among a formula the position isomer which interchanged, respectively among [A] four tetrapyrrole rings.)
[Formula 1]



[Claim 2] The object for an optical physicochemical diagnosis and/or the sensitizer for a therapy which consist of a porphyrin compound according to claim 1.
[Claim 3] The sensitizer for optical physical chemistry according to claim 2 used for a diagnosis and/or therapy of cancer.

[Translation done.]

Drawing selection drawing 1



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* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the drugs which use a porphyrin derivative, and the application and an especially new porphyrin derivative for the diagnosis and therapy of cancer by the sensitizer and/or the optical physical chemistry for the object for an optical physicochemical diagnosis, and a therapy which are made into an active principle.
[0002]
[Description of the Prior Art] The optical physicochemical diagnostic therapy (PDT) is performed as a new cure for cancer. After this prescribing a porphyrin compound of a certain kind for the patient by approaches, such as an intravenous injection, and making it hold it in a cancer organization, it irradiates laser light and it destroys only a cancer organization alternatively. PDT uses two properties in which the time amount held in the cancer organization of a porphyrin has the property in which it is long compared with normal tissue, and a photosensitization operation. In the past 15 years, 5000 or more people are treated for the malignant tumor by PDT all over the world, and it was established as one of the cancer treatments. Retina cancer, skin carcinoma, an esophagus cancer, superficialness vesical cancer, early lung cancer, etc. are going across the cancer type it is reported by PDT that good treatment results are variably.
[0003] The drugs currently used for current PDT are mainly a hematoporphyrin derivative (HPD) and photofrin. II**R They are (the ether object of HPD, and/or the dimer of an ester object). HPD is mixture which carries out vitriolization in an acetic acid of the hematoporphyrin, and is processed and obtained by 0.1 moreN sodium hydroxide. Moreover, photofrin II**R Although it ages ** 1995 and clinical application is carried out in Japan, the hydrophobic high component of HPD is mainly included, with HPD, it is complicated mixture and an active ingredient is unknown. Moreover, since the component ratio is not fixed, a curative effect is very unstable.
[0004] On the other hand, the new porphyrin derivative for PDT is indicated by [Br.J.Cancer, 55,483 (1987)] by JP,1-246286,A, No. 145283 [Showa 63 to], No. 205082 [Showa 62 to], No. 167783 [Showa 62 to], JP,62-249986,A, No. 246580 [Showa 62 to], No. 246579 [Showa 62 to], No. 205081 [Showa 62 to], and J.F.Evensen and others. Moreover, a porphyrin dimer derivative is indicated by a U.S. Pat. No. 4649151 number (1987), JP,62-63586,A, and No. 500132 [Showa 60 to, and the porphyrin metal complex is indicated for the chlorin derivative by JP,1-250381,A, No. 290881 / Showa 63 to, No. 5986 / Showa 62 to, No. 5985 / Showa 62 to, No. 5924 / Showa 62 to, No. 5912 / Showa 62 to, No. 981 / Showa 58 to /, and No. 185220 / Showa 57 to / at JP,1-221382,A, No. 104987 / Showa 63 to, and No. 31688 / Showa 57 to /. META tetra-hydroxyphenyl which very recently has absorption near 670nm Porphyrin derivatives, such as a chlorin (m-THPC) and a benzoporphyrin derivative (BPD), have also been developed. Many things were examined, the porphyrin metal complex has been indicated to JP,2-138280,A, No. 174079 [Showa 62 to], JP,4-24661,B, Taira No. 15545 [six to], and Taira No. 25763 [seven to], and we have also indicated the bacteriochlorin derivative for the chlorin derivative to JP,63-196586,A at JP,61-7279,A and No. 92287 [Showa 60 to]. However, utilization was [in / with the above-mentioned compound / composition, stability, and a water-soluble field] difficult for using as a sensitizer for PDT. Then, although it inquired further, the alkoxy porphyrin amino

acid derivative and the chlorin derivative were indicated to JP,5-97857,A and the effectiveness as a sensitizer for PDT was shown, the derivative with which a still higher curative effect is acquired is expected.

[0005] Moreover, there is also a problem of organization permeability of the laser light used for PDT. HPD and photofrin II**R ****** absorption wavelength is 630nm and a molar extinction coefficient is also as low as 3000. With 630nm light, organization permeability will be bad and will be limited to the surface cancer whose curative effect of PDT is 5-10mm.

[0006] On the other hand, there is a problem also in laser equipment. The dye laser present most often used has bad stability, and the handling on employment is difficult for it. Employment will become quite easy if titanium sapphire laser is used. However, HPD and Ptofrin which will be restricted to 670nm or more absorption wavelength of 600nm or less if this laser is used, and have the absorption wavelength near 630nm II**R being alike -- it is inapplicable. Recently, the compound which semiconductor laser (670nm) is also developed and has absorption in 670nm has been made advantageous.

[0007] Furthermore, causing photosensitivity temporary as a side effect of drugs is known. For this reason, after medication, a patient must be confined in a dark place for a long period of time so that normal tissues, such as the skin, may not be destroyed in a photosensitization operation. HPD and Ptofrin II**R Since the elimination rate from ********** is slow, when long, photosensitivity may remain six weeks or more. The drugs by which current use is carried out are holding the trouble of such many, and are HPD and Photofrin. II**R Development of the new drugs which are alike and replace is desired strongly. Then, the compound which is a single compound as what conquers the fault which the above-mentioned drugs have, and has absorption in a long wavelength field (650-800nm) more is proposed as a drug of the second generation. Various compounds, such as ring escape mold porphyrins, such as porphyrins, such as aza-porphyrins, such as a current phthalocyanine, and chlorin bacteriochlorin, and TEKISAFIRIN, are studied.

[0008]

[Problem(s) to be Solved by the Invention] With the good accumulation nature to stability and a cancer organization maintain, from normal tissue, the elimination rate reduced phototoxicity quickly, and when it could moreover do and having been got, it looked for the Bolu Phi Lynne derivative which can use titanium sapphire laser (670nm or more wavelength of 600nm or less), and semiconductor laser (670nm), and this invention persons be single components and repeated various researches for the purpose of offer the photosensitizer suitable for PDT.

[0009]

[Means for Solving the Problem] Consequently, it found out have the longest wavelength absorption end 670 morenm or more for eccritic [more prompt than the accumulation nature and normal tissue which be excellent in the single component to the cancer organization] in the side chain of the chlorins which carried out synthetic derivatization in the derivative (JP,5-97857,A) of application more nearly before than the protoporphyrin of the blood origin, when a certain kind of an imino group and aspartic acid residue be combine, and have the good PDT effectiveness.

[0010] Moreover, when, as for this invention persons, these chlorin derivative and the ultraviolet absorption (UV) spectrum of the mixture of albumin as well as the derivative (JP,5-97857,A) of application were analyzed before, it turned out that the trend of a spectrum has led to the compatibility to a positive direction, i.e., a specific organ, especially cancer.

[0011] On the other hand, this invention persons are [0012] having a strong operation turned out to be when the photosensitized oxidation using the system of a dansyl methionine substrate which can evaluate the reactant strength to light by thin-layer chromatography (TLC) or high performance chromatography (HPLC) simple before like the derivative (Japanese Patent Application No. No. 276488 [four to]) of application estimated these chlorin derivative. This invention is completed based on the above-mentioned knowledge, and the summary is the general formula -ization 1 (among a formula). (I) The porphyrin compound shown by the residue excluding [CH3, C2H5, CH2CH (CH3)2, CH2C6H5, CH2C6F5, and R2] hydrogen from the aspartic acid in R1 It expresses also (including [however,] the position isomer) with which the

functional group of the side chain of B ring interchanged among [A] four tetrapyrrole rings among the formula, respectively.

[0013] The porphyrin compound of this invention can be manufactured by the very thing conventionality. If it is in the porphyrin compound corresponding to a general formula (I), it derivatizes to the compound which has an aldehyde group first (process a), and the residue of an aspartic acid is made to combine (process b), and condensation of the various hydroxylamine derivatives is carried out to the obtained chlorin derivative (process c). Moreover, a process (b) and (c) may not carry out a sequential reaction, and as shown in (c) and (b), the order of a process may not necessarily replace them.

[0014] A configuration process (a) can perform this by the conventional approach indicated by J.E.Falk work [Porphyrins and Metalloporphyrins] (Elsevier issue, 1975), D.Dolphin work [The Porphyrins] (AcademicPress issue, 1978), etc.

[0015] For example, what is the porphyrin compound which has R1 and R2 corresponding to (I) should just prepare this according to the approach indicated by JP,61-7279,A, JP,63-13997,B, JP,6-15545,B, JP,7-25763,B, JP,2-138280,A, JP,4-59779,A, JP,5-97857,A, and Japanese Patent Application No. No. 323597 [three to]. That is, about (a), it is protoporphyrin a chlorin chemically-modified degree. The 1-hydroxy-2-formyl ethylidene-protoporphyrin dimethyl ester (henceforth P-Me) obtained by carrying out photochemical reaction processing of the dimethyl ester (henceforth PP-Me) is prepared (however, 3 which the functional group of the side chain of B ring replaced among [A] four tetrapyrrole rings, respectively - [A hydroxy-4-formyl ethylidene-protoporphyrin dimethyl ester object is also included.]).

[0016] Next, the joint process (b) of the residue of amino acid is given. That is, an aspartic acid is made to react to the porphyrin compound (I) whose R2 is a hydroxyl group, and R2 manufactures an aspartic-acid support porphyrin compound (I). By the conventional approach indicated by the Izumi store work [the foundation of peptide synthesis, and an experiment] (the Maruzen issue, 1985) etc., this thing can perform this and should just prepare this according to the approach indicated by JP,64-61481,A, JP,7-25763,B, JP,2-138280,A, and JP,4-59779,A.

[0017] In this case, since what is necessary is just to introduce the residue of an aspartic acid into the side chain of a porphyrin compound in short, it is desirable to advance a reaction between the carboxyl group of R2 side chain of (I) and the amino group of an aspartic acid, for this reason, the former carboxyl group and/or the latter amino group may be changed into a conventional reactant radical, or protecting suitably the functional group it is not desirable to participate in the reaction to which it exists in both may be taken into consideration. In addition, in any case, use of a reaction accelerator like a dehydrating agent or a deoxidizer or a condensing agent may also be suitably taken into consideration.

[0018] The chlorin compound constituted as mentioned above is given to a condensation process (c). A hydroxylamine derivative is made to react to P-Me, and a condensation product porphyrin compound is manufactured. This thing can perform this by the conventional approach indicated by the general organic chemistry experiment in the letter [the condensation reaction of a hydroxylamine and an aldehyde compound]. In addition, instead of compounding artificially, this may be extracted from a natural resource like vegetation or an animal.

[0019] Hereafter, the example of representation is given and preparation of a porphyrin compound (I) is explained still more concretely. For example, the 1-hydroxy-2-formyl ethylidene-protoporphyrin (it is called Following P) obtained by hydrolyzing P-Me is prepared (however, the functional group of the side chain of B ring also contains the 3-hydroxy-4-formyl ethylidene-protoporphyrin which interchanged, respectively among [A] four tetrapyrrole rings.). To this, it is an aspartic acid. Methyl ester etc. is made to react using a condensing agent (for example, [dicyclohexylcarbodiimide (DCC) and water-soluble cull POJIIMIDO (WSC)]) etc. in a solvent, and the porphyrin compound (I) which aspartic-acid residue combined with the side chain of R2 is obtained. Subsequently, hydroxylamine derivatives (for example, O-methyl hydroxylamine, O-ethyl hydroxylamine, O-benzyl hydroxylamine, etc.) are made to react using condensing agents (for example, a pyridine, a piperidine, an acid, alkali, etc.) in a solvent, and the porphyrin compound (I) which these compounds condensed in the side chain of R1 is obtained. The following can be mentioned as the example.

[0020] (1) 13 17-screw propionyl aspartic-acid-3-ethenyl-7-hydroxy-8-methoxy imino ethylidene - 2, 7, 12, 18-tetramethyl-porphin (henceforth NOMe-P-diAsp)
(2) 13 17-screw propionyl aspartic-acid-3-ethenyl-7-hydroxy-8-ethoxy imino ethylidene - 2, 7, 12, 18-tetramethyl-porphin (henceforth NOEt-P-diAsp)
(3) 13, 17-screw propionyl aspartic acid -3 - Ethenyl-7-hydroxy-8-iso butoxy imino ethylidene - 2, 7, 12, 18-tetramethyl-porphin (henceforth NOisoBu-P-diAsp)
(4) 13 17-screw propionyl aspartic-acid-3-ethenyl-7-hydroxy-8-benzyloxy imino ethylidene - 2, 7, 12, 18-tetramethyl-porphin (henceforth NOCH2C6H5-P-diAsp)
(5) 13, 17-screw propionyl aspartic acid -3 - Ethenyl-7-hydroxy-8-pentafluoro benzyloxy imino ethylidene - 2, 7, 12, 18-tetramethyl-porphin (henceforth NOCH2C6F5-P-diAsp)
[0021] What is necessary is just to perform manufacture of the drugs pharmaceutical preparation of the porphyrin derivative by this invention by the the very thing well-known method, and to dissolve the derivative by this invention with the suitable buffer solution. The solubilizing agent (for example, organic solvent) which uses as a suitable additive, for example, can be admitted in physic, pH modifier (for example, an acid, a base, the buffer solution), a stabilizer (for example, ascorbic acid), an excipient (for example, glucose), an isotonizing agent (for example, sodium chloride), etc. may be blended.
[0022] the drugs by this invention -- the need as drugs for PDT -- the compatibility over albumin, sufficient property, i.e., long phosphorescence life, a specific organ especially the specific accumulation nature to cancer, the optical killer cell effectiveness by dansyl methionine evaluation, absorption wavelength, water solubility, purity, etc. are satisfied enough. The good water solubility of the drugs by this invention enables manufacture of a high concentration solution (50mg/(ml)), and the drugs by this invention show high stability further not only in the inside of a test tube but in the living body. Generally, in order to apply as drugs for PDT, it is desirable to prescribe the drugs of this invention for the patient in the amount of 1mg - 5 mg/kg weight.
[0023]
[Function] The porphyrin compound concerning this invention has the description on the chemical structure at the point of having amino acid residue or an aldehyde condensation product in the side chain of a porphyrin frame, and, as a result, demonstrates various physiological or pharmacological profiles.
[0024] A cancer cell is piled up alternatively and these porphyrins derivative has the slow elimination from a cancer cell. In addition, from a normal organ or a cell, since it is excreted promptly, damage is not done to them. Originally, although the thing of ****** of a porphyrin derivative had the strong operation to light, while it raised excretory [from normal tissue] by introducing polyfunctional compound residue into the side chain of a porphyrin derivative according to this invention, the derivative of it designed so that a phototoxic manifestation might be controlled as much as possible became possible. Moreover, when chlorin derivatization of the porphyrin was carried out and wavelength carried out a red shift, the degrees of ** of a curative effect were able to be measured. The porphyrin derivative of this invention is useful as PDT drugs [as opposed to an organ especially specific cancer, or a specific malignant tumor based on these properties (cancer compatibility, the optical killer cell effectiveness, absorption wavelength, water solubility)].
[0025] An example is given and explained below. In addition, all the yield in an example is the values converted and calculated from PP-Me which is a start raw material.
[0026]
[Example]
example synthetic R.K of 1P -- it compounded according to Dinello's and others approach [The Porphyrins, Academic Press issue, and Vol.1,303 (1978)]. PP-Me100g was dissolved in chloroform 10l., and it was made to react for one week under an optical exposure. (From a porphyrin to chlorin derivatization) After [a reaction] vacuum concentration was carried out and residue was obtained. The obtained residue was refined in silica gel column chromatography - (eluate: n-hexane-chloroform), and P-Me was obtained. (50.0g) Then, this was hydrolyzed in pyridine methanol mixture and P of a dark green crystal was obtained. (43.0g, 42.7% of yield)

[0027] Example P2g obtained in the aspartic-acid derivatization example 1 of two porphyrins was dissolved in the tetrahydrofuran, and it considered as the P-DCHA salt (2.0g) with the conventional method in dicyclohexylamine (DCHA). This DCHA salt is dissolved in chloroform 150ml, and it is an aspartic acid. 2g of dimethyl ester (AspMe) hydrochlorides was added, and you added water-soluble carbodiimide (WSC) 2g gradually to the bottom of churning, and made it react for 1.5 hours. Vacuum concentration of the chloroform layer was carried out for reaction mixture after rinsing liquid separation after the reaction (a reaction end point is checked in TLC). Reprecipitation and recrystallization were repeated in the ethyl-acetate-ether-n-hexane, the obtained concentrate was performed, and photograph pro TOPORUFINIRU -6 of a dark green crystal and 7-screw aspartic-acid tetramethyl ester (henceforth P-AspMe) were obtained. (1.2g, 17.3% of yield)

[0028] example P-AspMe500mg obtained in the synthetic example 2 of 3 NOMe-P-diAsp (1) -- pyridine 20ml -- dissolving -- the bottom of room temperature churning -- 150mg of O-methyl hydroxylamine hydrochlorides -- addition -- you made it react for 30 minutes Chloroform was added to reaction mixture after the reaction, and vacuum concentration of the chloroform layer after rinsing liquid separation was carried out. The obtained concentrate was reprecipitated in the ethyl-acetate-n-hexane, precipitate was dissolved in pyridine 10ml after separation desiccation, and it hydrolyzed by adding 10ml of 1-N sodium hydroxides. Liquids were separated under chloroform after neutralization with 1-N hydrochloric acid, and vacuum concentration of the chloroform layer was carried out. The concentrate was reprecipitated in the methanol-ethyl-acetate-n-hexane and NOMe-P-diAsp (1) of a dark green crystal was obtained. (390mg, 13.9%)

[0029] example P-AspMe500mg obtained in the synthetic example 2 of 4 NOEt-P-diAsp (2) -- pyridine 20ml -- dissolving -- the bottom of room temperature churning -- 150mg of O-ethyl hydroxylamine hydrochlorides -- addition -- you made it react for 30 minutes Chloroform was added to reaction mixture after the reaction, and vacuum concentration of the chloroform layer after rinsing liquid separation was carried out. The obtained concentrate was reprecipitated in the ethyl-acetate-n-hexane, precipitate was dissolved in pyridine 10ml after separation desiccation, and it hydrolyzed by adding 10ml of 1-N sodium hydroxides. Liquids were separated under chloroform after neutralization with 1-N hydrochloric acid, and vacuum concentration of the chloroform layer was carried out. The concentrate was reprecipitated in the methanol-ethyl-acetate-n-hexane and NOEt-P-diAsp (2) of a dark green crystal was obtained. (420mg, 14.8%)

[0030] example P-AspMe500mg obtained in the synthetic example 2 of 5 NOisoBu-P-diAsp (3) -- pyridine 20ml -- dissolving -- the bottom of room temperature churning -- 150mg of O-isobutyl hydroxylamine hydrochlorides -- addition -- you made it react for 30 minutes Chloroform was added to reaction mixture after the reaction, and vacuum concentration of the chloroform layer after rinsing liquid separation was carried out. The obtained concentrate was reprecipitated in the ethyl-acetate-n-hexane, precipitate was dissolved in pyridine 10ml after separation desiccation, and it hydrolyzed by adding 10ml of 1-N sodium hydroxides. Liquids were separated under chloroform after neutralization with 1-N hydrochloric acid, and vacuum concentration of the chloroform layer was carried out. The concentrate was reprecipitated in the methanol-ethyl-acetate-n-hexane and NOisoBu-P-diAsp (3) of a dark green crystal was obtained. (450mg, 15.3%)

[0031] example P-AspMe500mg obtained in the synthetic example 2 of 6NOCH2C6H5-P-diAsp (4) -- pyridine 20ml -- dissolving -- the bottom of room temperature churning -- 150mg of O-benzyl hydroxylamine hydrochlorides -- addition -- you made it react for 60 minutes Chloroform was added to reaction mixture after the reaction, and vacuum concentration of the chloroform layer after rinsing liquid separation was carried out. The obtained concentrate was reprecipitated in the ethyl-acetate-n-hexane, precipitate was dissolved in pyridine 10ml after separation desiccation, and it hydrolyzed by adding 10ml of 1-N sodium hydroxides. Liquids were separated under chloroform after neutralization with 1-N hydrochloric acid, and vacuum concentration of the chloroform layer was carried out. The concentrate was reprecipitated in the methanol-ethyl-acetate-n-hexane and NOCH2C6H5-P-diAsp (4) of a dark green crystal was obtained. (400mg, 13.1%)

[0032] example P-AspMe500mg obtained in the synthetic example 2 of 7NOCH2C6F5-P-diAsp

(5) — pyridine 20ml -- dissolving -- the bottom of room temperature churning -- 150mg of O-(pentafluoro benzyl) hydroxylamine hydrochlorides -- addition -- you made it react for 120 minutes Chloroform was added to reaction mixture after the reaction, and vacuum concentration of the chloroform layer after rinsing liquid separation was carried out. The obtained concentrate was reprecipitated in the ethyl-acetate-n-hexane, precipitate was dissolved in pyridine 10ml after separation desiccation, and it hydrolyzed by adding 10ml of 1-N sodium hydroxides. Liquids were separated under chloroform after neutralization with 1-N hydrochloric acid, and vacuum concentration of the chloroform layer was carried out. The concentrate was reprecipitated in the methanol-ethyl-acetate-n-hexane and NOCH2C6F5-P-diAsp (5) of a dark green crystal was obtained. (390mg, 11.7%)

[0033] Example Laser radiation in 8 extraction organs (excitation fluorescence spectrum) 5mg test drug NOMe-P-diAsp (1) diluted with the phosphate buffer solution (1ml) to the golden hamster (one groups [five]) on 14 - the 21st which transplanted the pancreatic cancer cell of nitrosamine oncogenesis After intravenous injection, It is N2-pulsed to each organ which extracted each organ including cancer and was obtained. The exposure and the excitation fluorescence spectrum were measured for laser (N2,337nm, 2ns, 400-1000nm), and the wavelength of 600-900nm was examined on the basis of the peak wavelength of 470nm NADH. (N2-PLS measurement) The result (cancer / each organ ratio) obtained like the following is shown in Table 1. Table 1 measures each excitation fluorescence spectrum of each organ extracted 3 hours after medication, and shows the value which computed the peak wavelength in 600-900nm by making peak wavelength of 470nm into criteria 1.

[0034]

[Table 1]

化合物名	癌／臓器			
	癌／肝	癌／肺	癌／腎	癌／血清
(1) NOMe-P-diAsp	0.16	0.91	0.25	1.07
(2) NOEt-P-diAsp	1.16	-	6.70	0.32
(4) $NOCH_2C_6H_5$-P-diAsp	1.84	17.0	34.0	5.40
(5) $NOCH_2C_6F_5$-P-diAsp	2.80	14.0	2.80	0.07

[0035] Example 10micro (dansyl methionine) of evaluation substrates M of photosensitized oxidation using 9 dansyl methionine is dissolved in chloroform 1ml, 0.1micro of sensitizers M obtained in said example is added, and it is Cold under stirring. Spot It irradiated by PICL-SX (Nippon P.I.Co..Ltd.) (a halogen lamp, 150W, 80,000Lux). The spot of the reaction mixture was carried out to the TLC plate (Kieselgel 60 F254) for every optical exposure part, the expansion back was checked with the chloroform-methanol (3:2) and a dansyl methionine and its oxidation product (dansyl methionine sulfoxide) were checked with UV lamp (254nm). Time amount to which the dansyl methionine disappeared completely was made into reaction end time on the TLC plate, and comparison examination of the strength of the photooxidation reaction of each sensitizer was carried out. The result is shown in drawing 1 and Table 2. In addition, the axis of ordinate in drawing 1 shows Rf, an axis of abscissa shows time amount (minute), Rf value 0.79 is a dansyl methionine and 0.43 is a dansyl methionine. It is the spot of a sulfoxide. Moreover, the numeric value of Table 2 shows the completion time amount of a reaction by the part, and means that a photooxidation reaction is stronger as this value (minute) is small.

[0036]

[Table 2]

化合物名	光反応の強さ
PhotofrinII®	10<
(1) NOMe-P-diAsp	4
(2) NOEt-P-diAsp	4
(3) NOisoBu-P-diAsp	4
(4) $NOCH_2C_6H_5$-P-diAsp	4
(5) $NOCH_2C_6F_5$-P-diAsp	4

[0037] Example 10 ultraviolet-absorption analysis of a spectrum (albumin test)
It is known that a porphyrin compound will form two monomers or a polymer in an albumin solution. This property can be understood by migration of an absorption maximum value or fluctuation of an absorbancy index being seen by analyzing by changing various albumin concentration. Therefore, it is an easy screening test for examining compatibility with a cancer cell. Albumin 54mg is dissolved in a 3ml physiological saline, and it considers as concentration 1.8%. Subsequently, the liquid which diluted this 10 times and was made into 0.18% was diluted with the common ratio 3, and the liquid of each albumin concentration (1.8, 0.18, 0.06, 0.02, 0.0066, 0.0022%) was prepared. On the other hand, 1mg of porphyrin derivatives was dissolved in 1ml (pH8.0) of phosphate buffer solutions, and it was made 100ml with the physiological saline. And 2ml of albumin diluents and 2ml of porphyrin solutions were mixed, the albumin last concentration of mixture was made into 0.9, 0.09, 0.03, 0.01, 0.0033, and 0.0011%, and ultraviolet absorption spectrum measurement (350-900nm) was performed. Moreover, it measured similarly in a physiological saline and methanol solution instead of the albumin diluent. These measurement results are shown in Table 3. As the example of representation, the ultraviolet absorption spectrum of NOMe-P-diAsp (1) is shown in drawing 2 and drawing 3 .
[0038]
[Table 3]

化合物名	波長 (nm)		
	生理食塩水	メタノール	0.9 %アルブミン
(1) NOMe-P-diAsp	665	667	670
(2) NOEt-P-diAsp	665	667	670
(3) NOisoBu-P-diAsp	665	667	670
(4) $NOCH_2C_6H_5$-P-diAsp	666	667	670
(5) $NOCH_2C_6F_5$-P-diAsp	666	666	670

[0039] Example The infrared absorption spectrum of this derivative was measured with the KBr briquette method with 11 infrared-absorption-spectrum analysis infrared spectrophotometer. As the example of representation, the infrared absorption spectrum of NOEt-P-diAsp (2) is shown

in drawing 4 .
[0040]
[Effect of the Invention] Since the porphyrin derivative of this invention has the accumulation nature to a cancer cell, the reactivity over external energy, and a destructive operation of a cancer cell and moreover does not discover toxicity to a normal cell, it reaches [as cancer treatment medicine or a cancer diagnostic drug] to an extreme and is useful.

[Translation done.]